State of the science review: Advances in pain management in wounded service members over a decade at war

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ABSTRACT: The pain conditions and comorbidities experienced by injured service members and the challenge of pain management by the military medical system offer a unique opportunity to inform pain management and medical research. In this article, acute and chronic pain issues, current treatment options and limitations, as well as novel approaches to pain management are discussed within the context of combat casualty care, from the battlefield to hospitalization and rehabilitation. This review will also highlight the current pain management limitations that need to be addressed in future clinical and basic science research to improve care for our nation's injured service members. (*J Trauma Acute Care Surg*. 2014;77: S228–S236. Copyright © 2014 by Lippincott Williams & Wilkins)

During the last 12 years, during the span of Operation Enduring Freedom (OEF) in Afghanistan and Operation Iraqi Freedom (OIF), advances in battlefield medical techniques,[1] protective armor,[2] and rapid evacuation[3] have led to an impressive greater than 90% survival rate.[4] Of the injuries incurred on the battlefield to date, approximately 52,022 service members have been wounded in action, while 5,346 have sustained fatal injuries.[5] While this is a major improvement in survival, this substantially increases the number of patients needing treatment for significant pain.

Collecting data on acute pain and outcomes is challenging in combat zones because of prioritization of lifesaving interventions and rapid patient transition between ground and air transportation; therefore, reports are limited. One study on wounded soldiers being evacuated from Iraq and Afghanistan reported an average pain rating of 5.3 of 10 and worse pain rating of 6.8 during air evacuation, with 65% reporting inadequate pain relief during transport.[6] Within 24 hours of hospitalization, the average pain rating was 4.1 and worse pain rating of 7.4, with one third reporting 50% or less pain relief.[6] The pain experienced by returning service members remains significant as evidenced by a cohort of 162 soldiers being treated at Walter Reed Army Medical Center reporting an average pain rating of 5.9.[7] Another cohort of 50 soldiers treated at an inpatient polytrauma rehabilitation center reported an average pain score of 5.6 with a mean duration of 83 days of pain at the time of admission and an average pain score of 3.7 at discharge.[8] Clinically significant pain persists into the veteran population as evidenced by a cohort of 369 veterans being treated at a VA medical center with 59% reporting pain intensity level of 4 or higher.[9] Comorbidities, such as posttraumatic stress disorder (PTSD), traumatic brain injury, insomnia, and depression, further complicate the pain management regimen. In a cohort of 340 OIF/OEF veterans, 82% reported chronic pain, 68% were diagnosed with PTSD, and 67% were diagnosed with persistent postconcussive symptoms following traumatic brain injury.[10] Of these veterans, 42% were diagnosed with all three conditions simultaneously.

With this review, we will attempt for the first time to summarize many of the issues and the information collected in the last 12 years of conflict surrounding the management of pain in this newly expanded population of injured service members. An overview of current limitations to pain management that need to be addressed to improve care will be provided. In addition, novel approaches to pain management of interest to military medicine will be discussed.

Current State of Pain Management From the Battlefield to the Hospital

When a service member is injured on the battlefield, the first medical attention received, known as Level I care, consists of self-aid, buddy aid, or care administered by the combat medic. Once removed from the battlefield, the service member undergoes resuscitation and stabilization for rapid ground or air transportation to a Level II care facility, which is staffed by a Forward Surgical Team or a Level III combat support hospital.[11] If deemed unlikely to immediately return to duty, the injured service member is then air evacuated to a definitive care facility (Fig. 1). The following sections discuss the current pain management priorities and complications at each level of care.

Levels I to II: First-Responder Pain Management on the Battlefield

Pain management immediately following combat trauma is often deprioritized next to resuscitation and stabilization for rapid transport of the trauma patient. Furthermore, collection of

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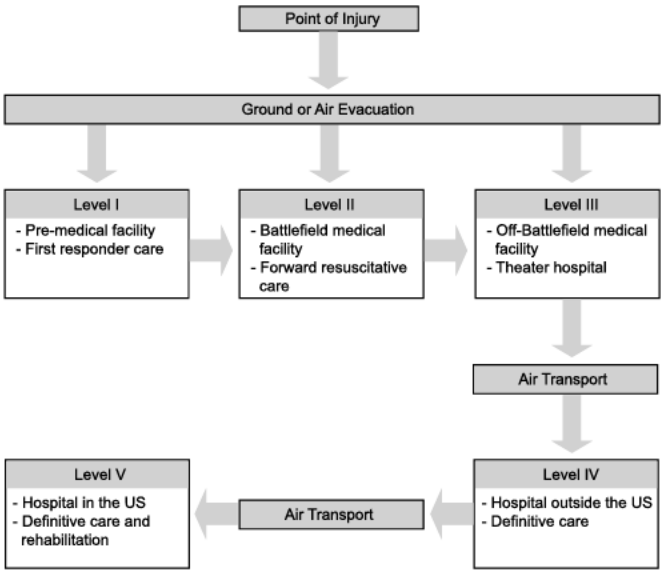

Figure 1. Schematic illustrating injured service member movement through the continuum of care.

data reporting analgesic use is complicated by the treatment of traumatic injuries in an austere environment with multiple patient transfers.[8] The most common medications carried by the service member are nonsteroidal anti-inflammatory medications, including meloxicam and acetaminophen.[12] The combat medic has access to additional analgesics, potentially including both opioid and nonopioid analgesics to be given if the service member can no longer remain in combat.[13] If intravenous or intraosseous access is not obtainable or is not required, the medic can administer intramuscular morphine via an autoinjector mechanism. Other analgesic possibilities not requiring intravenous/intraosseous access include oral transmucosal fentanyl or intramuscular ketamine.

However, opioid-induced respiratory depression and decreased cardiovascular function limit opioid use in wounded service members with hypovolemic shock.[14] Because of the nature of combat injuries sustained in current overseas contingency operations, this includes a significant percentage of severely wounded service members, creating a major barrier to pain management on the battlefield. In addition, the analgesic efficacy of morphine and other drugs given intramuscularly is also significantly reduced during hypovolemic shock as blood is shunted away from the limbs to maintain organ function preventing intramuscularly administered drugs from entering circulation efficiently.[15] The lack of pain relief may also lead the medic to administer additional doses of medication, resulting in the simultaneous central nervous system availability of a large amount of analgesic following resuscitation. This may lead to additional adverse effects and perhaps necessitate the use of additional medications to counteract these effects.

Opioid-induced dysphoria and dyskinesia,[6] which are manageable in a traditional hospital setting, can be especially detrimental on the battlefield. If the injured service member experiences these effects, they may require assistance and monitoring from additional service members, thus reducing the force strength and increasing endangerment of the remaining members of the group. These effects can also make the evacuation of the casualty to a higher level of care more difficult because of their inability to participate actively in their own evacuation. To treat pain immediately on the battlefield and during evacuation, pain therapeutics must be easy for a combat medic to carry, have minimal abuse potential, be easy to quickly administer in an austere and dangerous environment, and have limited effects on cognition and motor function (Fig. 2).

In addition, a recent change has been made to the Tactical Combat Casualty Care (TCCC) guidelines, which simplifies previous battlefield analgesic recommendations.[16] It is now recommended that battlefield analgesia be achieved with a triple option of treatments as follows: (1) meloxicam and Tylenol for relatively minor pain, (2) oral transmucosal fentanyl for moderate-to-severe pain (without hemorrhagic shock or respiratory distress), and (3) ketamine for moderate-to-severe pain with hemorrhagic shock or respiratory distress.

Levels III to IV: Theater and Tertiary Hospital Pain Management

Combat casualties evacuated from theater are treated and stabilized at tertiary hospitals associated with the US Department of Defense. Pain management at these facilities must encompass acute injury–associated pain and postsurgical pain. It has been reported that upon hospitalization at either the Landstuhl Regional Army Medical Center (currently the only Level IV facility) or the Walter Reed Army Medical Center (Level V), 56% of the soldiers injured in OIF received nonsteroidal anti-inflammatory drugs, 49% were prescribed opioids, and 41% received an anticonvulsant or antidepressant.[7] A recent retrospective analysis conducted by our group at the US Army Institute of Surgical Research reported that the Top 3 analgesics given to alleviate pain in the most severely burned service members were fentanyl (94.1% of the patients), morphine (90.1%), and methadone (87.1%) (manuscript in preparation). While pain management options are not limited at this level of care, the nature of injuries often precludes the ability to provide opioids, and treatment must take into account the patient's overall pain goals balanced with the specific surgical needs.

Level V: Pain Management During Stateside Hospitalization and Rehabilitation

The transition to outpatient care can be challenging for the polytrauma patient. For those with a high opioid requirement, clear plans must be made for stabilizing the patient on a combination of pain medications that are appropriate for the outpatient setting. These may include not only short- and long-acting opioids but also anti-inflammatory agents, antidepressants, and various neuromodulators. Of a cohort of 50 soldiers admitted to an inpatient polytrauma rehabilitation center, 58% were administered with opioids, 50% were administered with nonsteroidal anti-inflammatory medications, and 20% received anticonvulsants.[8] The comprehensive interventional pain clinic has become a vital component of the medical treatment system built for the comprehensive care of every service member, whether injured in combat or otherwise in need of medical care.

Figure 2. Schematic illustrating special considerations for pain management of the combat wounded service member.

Recently, to provide a more uniform, evidence-based framework for management of pain, anxiety, and delirium in combat injured patients, an updated Clinical Practice Guideline has been issued by the Joint Theater Trauma System. Its recommendations include the development of an Acute Pain Service at Level III to V facilities and the use of a new DOD/VA Pain Rating Scale for assessing pain, the Richmond Agitation Sedation Scale for assessing anxiety, and the Confusion Assessment Method for assessing delirium. This Clinical Practice Guideline also describes multimodality pain therapy, details for use of epidural and peripheral nerve catheters, and other aspects of treatment for compartment syndrome, air evacuation, nursing care, pharmacy support, and performance improvement monitoring.

Pain Management Issues Specific to the Wounded Service Member

Risk of Pain Chronification and Comorbidities

It is now well-known that early management of pain is critical to reducing the prevalence of chronic pain conditions. Following combat trauma, however, resuscitation and stabilization are prioritized over pain management because administration of pain therapeutics such as opioids can cause respiratory depression and hypotension. Therefore, service members injured in combat are at a higher risk of pain chronification. Chronic pain, a continuous or recurrent condition lasting beyond the usual recovery time from acute injuries (by definition >3–6 months), affects mobility and other bodily functions, thereby adversely affecting quality of life.

The types of injuries incurred on the battlefield are polytraumatic, often requiring lengthy recovery times and aggressive pain management strategies. Optimal pain management in these cases is problematic in terms of analgesic availability and the ability to maintain adequate pain relief throughout treatment, recovery, and rehabilitation. Unfortunately, long-term use of opioids can lead to the development of tolerance potentially requiring dose escalation, which can increase the potential for dependence and misuse or abuse. However, if pain remains improperly managed, persistent stimulation of peripheral sensory neurons can cause increased excitability of central nociceptive pathways, leading to pain hypersensitivity and structural changes to various brain regions.[17] Whether this phenomenon is reversible is under debate. Amplification of pain signals through changes in the plasticity of nociceptive systems produce a heightened degree and duration of pain as well as an increase in the size of painful areas.

To reduce the development of chronic pain in injured service members, it is necessary to properly manage pain at the onset of injury, preferably on the battlefield, before the onset of central sensitization. Novel therapeutics and strategies that can act at the level of peripheral nociceptors, before central sensitization, may block the cellular and molecular mechanisms driving neuronal plasticity that lead to the development of these chronic pain conditions. Such therapies have the potential to limit or prevent the development of chronic pain conditions specific to the injured service member, such as lower back pain, neuropathies, and phantom limb pain associated with amputations. Furthermore, sufficient pain management is especially important during early wound healing, as pain during this period is associated with the patient's ability to adjust and cope with the injury up to 2 years following discharge.[18]

Early successful pain management may also decrease the incidence of psychological and psychosocial issues such as PTSD, depression, anxiety, and sleep problems. Managing pain at the onset of injury has been reported to decrease the risk of PTSD by inhibiting stress hormone release responsible for the facilitation of memory formation.[19] These comorbidities not only affect the patients' mental health but also are detrimental to their physical health.[20] Their presence can directly alter stress response and inflammation, leading to increased pain.[8,20] Moreover, many patients experience anxiety and fear, which can also lead to inflammatory cytokine production and increased pain.

Risk of the Development of Tolerance and Addiction

The development of tolerance and addiction poses a serious threat to service members, making this a top priority of the Office of the Army Surgeon General (Pain Management Task Force Report, May 2010). The unique challenges service members face as a patient population can predispose them to a heightened risk of developing addiction. Service members with depression or PTSD diagnoses have increased incidence

of alcohol and drug use disorders.[21] Whether the service member was exposed to combat while deployed can also increase the risk of addiction. The prevalence of alcohol abuse is higher in veterans than in the civilian population[21] and deployed personnel that report combat exposure are more likely to abuse alcohol.[22] Even the young age of the service member population is a predisposing factor with chronic opioid use in young veterans increasing from 3% in 2003 to 4.5% in 2007, while opioid use in veterans older than 50 years remains static.[23]

The development of tolerance to pain medications may be one mechanism that leads to addiction, as evidenced by the near tripling of prescription drug abuse among active duty military personnel between 2005 and 2008.[24] Opioid-based narcotics are among the most prevalent therapeutics for the management of severe pain in injured service members during hospitalization;[6] however, they are subject to the development of tolerance and dependence and have a high abuse potential. For example, the average duration of hospitalization of burned service members is 24 (±25) days.[25] Adult burn patients receiving intravenous benzodiazepines or opioids for as little as 7 days developed acute withdrawal symptoms when weaned off treatment,[26] which can trigger the onset of addiction. During prolonged exposure to opioids, compensatory neurochemical adaptations occur in the central nervous system, such as changes in axonal transport[27] and alterations of tyrosine hydroxylase immunoreactivity and phosphorylation specific to dopaminergic neurons of the reward pathway.[28] Prolonged exposure to opioids increases addiction-like behaviors in rats, while shorter access results in less addiction-like behaviors.[29] Upon drug cessation, there is a physiologic dysregulation that manifests into emotional and physiologic withdrawal symptoms, which can trigger aberrant drug-related behaviors as a means of compensation.[30] In support, chronic opioid exposure in rats leads to escalation of drug seeking and taking when administration has ceased.[31]

Therefore, withdrawal can serve as a powerful motivator of drug seeking and drug taking. Accordingly, substance abuse and aberrant drug-related behaviors are a major concern following cessation of chronic opioid treatment. Patients with a history of chronic pain and opioid consumption report higher pain scores, require longer acute pain services, and use more pain medication compared with patients without a history of chronic pain and opioid consumption.[32] It is therefore important to identify pain therapeutics that can be used across long-term hospitalization and rehabilitation with reduced risk of the development of tolerance, withdrawal, and addiction.

Future Directions for Pain Management in Wounded Service Members

Dual Mechanism Therapeutics

Antidepressants that target the neurotransmitters serotonin and norepinepherine, such as amytriptyline and duloxetine, have been proven successful in treating a variety of pain conditions[33,34] with the potential added benefits of mood elevation, sleep pattern normalization, and muscle relaxation. However, pain management with antidepressants has not been successful for all pain conditions and has not yet been shown to be successful for pain associated with traumatic injuries, indicating that the pain relieving properties of antidepressants alone may not be powerful enough to treat the types of pain experienced by service members. Alternatively, recent dual-mechanism therapeutics have been developed, which target both neurotransmitter mechanisms and opioid receptors simultaneously and may be successful in treating severe pain conditions. Two dual-mechanism therapeutics, tramadol and tapentadol, exert analgesic effects via combining μ-opioid receptor agonism and serotonin/norepinephrine reuptake inhibition.[35]

Preclinical research has reported that tramadol reduces postoperative pain[36] and tapentadol reduces acute and chronic inflammatory pain,[37] and we have recently shown that tramadol significantly attenuates pain behaviors in a rat model of full-thickness thermal injury.[38] Clinical research has found that tramadol and tapentadol are effective in treating arthritis, diabetic neuropathy, and postoperative pain with an opioid-sparing effect and reduced adverse effects.[39] A recent systemic review reported that the benefit-risk ratio of tapentadol is improved compared with Step 3 opioids for chronic severe pain.[40]

Importantly, dual-mechanism therapeutics may produce less tolerance development as they have reduced opioid receptor activity. It was recently reported that tapentadol produced greater pain relief with less adverse events compared with oxycodone.[40] Furthermore, there is evidence that antidepressants may be effective analgesics when administered peripherally,[41,42] thus avoiding centrally mediated negative adverse effects; however, this has not yet been examined with the dual-mechanism therapeutics tramadol or tapentadol. Newer-generation pain therapeutics that target dual mechanisms simultaneously may improve pain management in service members while reducing the development of tolerance with the potential added benefits of mood enhancement.

Targeting Glia to Attenuate Morphine Tolerance and Addiction

It is becoming increasingly clear that neurons are not the only cells in the central nervous system responding to pain. Glia, the supporting cells of the central nervous system, also respond to injury by releasing proinflammatory cytokines, nitric oxide, prostaglandins, and excitatory amino acids,[43,44] which lessens the efficacy of morphine analgesia.[45] Glia activation during polytraumatic injuries may play a role in further enhancing pain in injured service members. As chronic morphine administration is known to activate glia[46,47] and further evoke glial release of cytokines,[48] glia have the potential to both enhance pain and significantly reduce morphine efficacy in wounded service members receiving lengthy pain management with opioids.

Glial activation may also lead to the development of tolerance to opioid analgesics.[49] Morphine administration has been found to specifically activate glia in the reward pathway,[46] increasing its excitability,[50] which may be a factor in the development of addiction. Therefore, inhibiting glia activation may reduce its effects on enhancing pain, reducing morphine analgesia, inducing morphine tolerance, and reducing the activation of reward pathways that may initiate addiction.

Recent studies have identified several substances that inhibit glial activation such as minocycline,[51] AV411,[52] as well

as naloxone and naltrexone.[53] Because the μ-opioid receptor is stereospecific to the (−) isoform, and both the (−) and (+) isoforms inhibit glial activation, the (+) isoforms can be used to inhibit glial activation, without effecting opioid receptor binding. Accordingly, the use of glial activation inhibitors may play a significant role in the treatment of pain as attenuation of neuropathic pain has been found as a result of administration of minocycline[51] and (+) naloxone.[53] In addition to the reduction of pain, the inhibition of glial activation increases the analgesic efficacy of morphine,[54] reduces the reward value of morphine,[55] and attenuates morphine tolerance.[56] Therefore, glial inhibition may serve as a useful therapeutic tool to enhance pain relief while also lessening the development of opioid tolerance and the propensity for addiction.

Peripheral Opioid Analgesia

There are several advantages of peripherally acting analgesics including the following: maximum efficacy can be achieved with low (below systemic) doses, therapeutics can be administered in many forms (lotion, powder, gel, patches, or aerosol), they avoid action at central sites by not crossing the blood-brain barrier, drug metabolism and interactions are minimal, drug can be released in a controlled manner at the site of injury, and ease of access for repeated application.[57] Following injury, the nerve endings of primary sensory neurons innervating the affected tissues are the initial generators of noxious impulses. As these neurons become sensitized following repetitive noxious input, the development of hyperalgesia (heightened sensitivity to noxious stimuli) and allodynia (developed sensitivity to nonnoxious stimuli) is observed. An effective peripherally acting analgesic drug prevents sensitization of peripheral afferents and successive central events.

Both preclinical and clinical studies indicate efficacy for peripheral opioid analgesia. Direct administration of ultralow doses of opioids at the site of inflammation produces analgesia without adverse effects.[58] Peripheral opioid analgesia occurs via the μ-opioid receptor, which is up-regulated in both the primary neuronal cell bodies of the dorsal root ganglia and along their peripheral nerve endings following inflammation. In addition, inflammatory cells that are transported into the inflamed area also release endogenous opioids, such as β-endorphins, in response to both exogenous and endogenous stimuli.[59]

While the military medical system does not currently use peripheral opioid analgesia, this pain management technique may prove beneficial in wounded service members. Reaching optimal opioid analgesia while avoiding central nervous system–mediated adverse effects would provide a way to treat pain associated with combat trauma while not creating an additional barrier to lifesaving medical care and resuscitation.

Nonopioid Peripheral Analgesia

Peripheral, nonopioid targets for analgesia are limited; however, one potential target may be the transient receptor potential V1 (TRPV1) ion channel, a peripheral pain generator.[60] TRPV1 is highly localized on nociceptive sensory neurons and their peripheral afferents and is activated by noxious stimuli, including heat and inflammatory mediators. TRPV1 activation initiates the pain processing signal to the central nervous system and can be sensitized by local inflammatory mediators in the damaged area to reduce the threshold for activation by noxious and nonnoxious stimuli.[61,62] This is clinically observed as heightened sensitivity to painful stimuli as well as developed sensitivity to innocuous stimuli, such that a nonnoxious touch, becomes painful.

Activation of TRPV1 induces a transient hyperalgesic response that is followed by desensitization of TRPV1, thus dampening pain processing. TRPV1 agonist-induced desensitization can be used for pain relief, such as that observed with topical capsaicin.[63] Furthermore, high concentrations of TRPV1 agonists desensitize TRPV1-expressing nerve endings to such a degree that they are temporarily ablated. Preclinical testing has reported that reversible ablation of TRPV1-expressing nerve fibers attenuates nociceptive transmission,[64,65] without affecting proprioception or motor controls.[66] The use of capsaicin has had limited success because of efficacy and compliance problems associated with their transient algesic effects at the time of application and need for reapplication several times a day for several weeks.[67] Resiniferatoxin (RTX) is an ultrapotent agonist to TRPV1 that ablates TRPV1-expressing nociceptive nerve fibers in peripheral tissues for weeks.[65] Preclinical research has found that RTX treatment is an effective analgesic for basal pain behaviors and inflammation-evoked thermal hyperalgesia in rats[65,66] and is currently in clinical trials as a cancer pain analgesic.[68]

RTX may also be an effective therapeutic for burn pain and pain associated with other traumatic injuries, incurred on the battlefield by service members. Our preliminary data in a rat model of burn pain indicate that RTX treatment reverses thermal hyperalgesia as early as 2.5 hours after injection. This medical technique has the potential to reduce the prevalence of chronic pain conditions as early blockade of pain signals have been reported to attenuate the transition from acute to chronic pain.[69] Having the medical technology to prevent pain detection for weeks following a traumatic burn or blast injury on the battlefield and during hospitalization would aid service members in safe evacuation with limited effects on motor coordination, optimize pain control, increase return-to-duty rates, and reduce the risk of addiction through reduced reliance on opioids.

Peripheral inflammation greatly alters a number of receptors and ion channels present on the primary sensory nerve fibers. Modification of TRP channels, acid-sensing receptors, glutaminergic (NMDA and AMPA/kainate) receptors, and voltage-dependent sodium channels contributes to the development of allodynia and hyperalgesia, and studies have shown that topical application of analgesics that mediate their actions through these receptors and ion channels attenuate pain.[63]

Increased Use of Regional Anesthesia

Regional anesthesia is currently used by the military medical system across the continuum of combat casualty care and is now part of the armamentarium to combat severe posttraumatic pain. It has its greatest use in the surgical repair of extremity wounds for preoperative, intraoperative, or postoperative analgesia or any combination of these. Regional and epidural anesthesia are typically first made available at

Level III. Level II facilities conduct mainly damage-control surgery, which is performed rapidly and is immediately followed by a transport to a Level III facility. Moreover, Level II facilities have limited blood banking capability, have limited access to blood component therapies, and are generally not equipped to deal with risks such as hematoma, which are associated with the placement of regional or epidural catheters. Other risks include a masking of pain that would impair diagnosis of the injury, potential nerve damage, infection through the catheter, drop in blood pressure, compartment syndrome in extremity-injured patients, and severe headache in the case of spinal nerve block. However, these are often outweighed by the benefits, which include superior analgesia at the injured site, unimpaired ventilatory control, hemodynamic stability, improved regional blood flow, reduced metabolic effects, improved immune function, maintenance of mental clarity, and others. The use of a continuous peripheral nerve block (CPNB) catheter in a combat casualty was first described in 2004;[70] however, single-shot peripheral nerve blocks and longer-term epidural catheters were likely in use before 2004. In 2009, the results of a survey of soldiers at Landstuhl Regional Medical Center who had received regional anesthesia, and specifically CPNB, showed significantly improved pain relief compared with controls (no CPNB).[6] In 2010, the Joint Improvised Explosive Device Defeat Organization (JIEDDO), a jointly operated organization within the Department of Defense dedicated to reducing or eliminating the effects of IEDs, initiated the successful use of high-definition ultrasound machines for insertion of peripheral nerve block catheters for wounded service members in OEF, before transport from the theater.

Pharmacogenetics Approach

Transgenic and knockout mice studies have shown that genetics and environmental factors play an important role in the modulation of pain perception and/or analgesia[71] such that an individual's genotype may predispose them to certain pain sensitivities and conditions. Polymorphisms in the catechol-O-methyltransferase (COMT) gene, encoding the primary enzyme for the catecholamines, have been implicated as a genetic predictor of acute sensation and the development of chronic pain conditions.[72] McLean et al. have associated genetic variation of COMT with higher intensity of postmusculoskeletal neck pain in patients experiencing motor vehicle collision and for individual pain outcomes in burn patients.[73,74]

Pharmacogenomics may provide a greater understanding of the relationship between opioid analgesics and individual pain management needs. A recent study, comparing monozygotic and dizygotic twin pairs, demonstrated the statistically significant contribution of genetic factors in intersubject differences in levels of opioid analgesia[75] and their aversive and reinforcing effects.[76] Other pharmacogenomic studies in both animals and humans have identified variations of the μ-opioid receptor gene (OPRM1) that account for variations in pain, opioid effectiveness, and dependency.[77,78] Although only one μ-opioid receptor gene has been identified, more than 100 genetic polymorphisms have been identified in humans. This provides an explanation for the wide range of potencies, effectiveness, and adverse effects observed with opioid treatment in the clinic.[78]

In addition to mutations in the COMT and the OPRM1 genes, single-nucleotide polymorphisms in genes encoding other drug-metabolizing enzymes, ion channels, receptors, and transporters have also been identified, and some of these have been linked to differences in analgesic drug responses.[79] Several single-nucleotide polymorphisms in the glucocorticoid receptor co-chaperone protein, called FK506 binding protein 5 (FKBP5), showed statistically significant association with overall pain and neck pain in patients 6 weeks after exposure to two distinct types of trauma, motor vehicle crash, and sexual assault.[80] The CYP2D6 gene, a cytochrome P450 drug metabolizing enzyme, is also highly polymorphic, with more than 50 mutations and 100 different alleles identified to date. Individuals have been identified with alleles conferring reduced CYP2D6 activity (poor metabolizers), normal activity (extensive metabolizers), and very high activity (ultrahigh metabolizers). In the case of two relatively weak μ-opioid receptor agonists that are activated by CYP2D6, codeine and tramadol, poor metabolizers typically experienced inadequate analgesia, while ultrahigh metabolizers experienced quicker than normal responses to these drugs but were also prone to higher toxicities.

As observed in the civilian population, military personnel with acute and chronic pain exhibit highly variable degrees of withdrawal, dependency, and tolerance for opioids and other analgesic drugs. Pharmacogenomic studies demonstrate that an individual's response to analgesic treatment is the result of a complex interplay between hereditary and environmental factors and that identifying one's genotype will eventually allow prediction of the efficacy and adverse effects of analgesic drugs. Pharmacogenetics and pharmacogenomics may allow personalized medicine for individual service members based on their genetic constitution.

Complimentary and Alternative Medicine for Pain Therapy

The Pain Management Task Force of The Army Office of the Surgeon General published a report in May 2010 calling for an increased use of complementary and alternative medicine (CAM) as an adjunct therapy to pharmaceuticals to relieve pain. One form of CAM that is currently of interest for use on the battlefield for pain management is acupuncture. Magnetic resonance imaging has shown that areas of the brain known to be involved in pain processing are altered during acupuncture compared with controls.[81] One pilot study reported that 23% of patients receiving auricular (ear) acupuncture in an outpatient setting reported a reduction in lower back, head, or neck pain.[82] Many theories have been postulated concerning the biologic effects of acupuncture to explain its ability to control pain, including the gate control theory.[83] According to this theory, acupuncture exerts pain relief by stimulating specific acupuncture points with a steady stream of nonpainful impulses transmitted to the spinal cord to block C fiber transmission for pain relief.[83] This theory however does not explain the long-term effects that are often observed in acupuncture pain treatment. In addition, studies have shown that acupuncture

releases local endorphins to produce analgesia.[84] However, the analgesic effects of acupuncture are typically more rapid than the release of endorphins.

Another promising CAM currently of interest is the use of immersion virtual reality (VR) during painful procedures to reduce excessive pain nonpharmacologically via an attentional mechanism.[85] Researchers consistently report 30% to 50% reductions in pain ratings when VR is used adjunctively with opioids during severe burn wound care.[86] Burn patients report spending less time thinking about their pain during wound care while using VR,[86,87] and there is a dose-response relationship between the immersiveness of the VR system and pain reduction.[88] In addition, fluorescence magnetic resonance imaging has shown significant reductions in pain-related brain activity associated with the use of VR,[85] which has been reported to be comparable with a moderate dose of hydromorphone[89] and optimal when VR and opioids were combined.

Encouraging results from studies on yoga for conditions such as a pain associated with osteoarthritis[90] has attracted attention from clinicians across military medical care. In support, physical exercise can stimulate the release of endocannabinoids,[91] and meditation can decrease the brain's sensitivity to incoming pain signals.[92] Yoga has been shown to reduce pain and disability and improve strength, balance, and gait in patients with arthritis.[93,94] A recent systemic review and meta-analysis reported evidence of short- and long-term effectiveness of yoga for patients with chronic lower back pain.[95] In addition, patients who were treated with yoga in addition to the normal physiotherapy exercises had significantly lower-state anxiety and trait anxiety scores and demonstrated less activation of their autonomic nervous systems as measured by blood pressure and pulse rates.[96] Massage therapy may also be a potential CAM therapy useful as adjunctive pain management;[97] however, there is inconsistent evidence supporting its effectiveness. The mechanism of pain relief by massage therapy is currently unknown, with hypotheses including gate control, effects on serotonin, and restoration of sleep.[98,99] Furthermore, beneficial effects on a variety of physiologic effects have reported, including increased local blood flow and cardiac stroke volume, increased lymph drainage, and anticoagulation effects.[100]

SUMMARY

Service members represent a special trauma patient population that is particularly vulnerable to pain chronification, complications with comorbidities, and the development of tolerance and addiction to opioid analgesics. Current pain management research aimed at avoiding these issues in service members includes evaluating the efficacy of dual-mechanism therapeutics for polytrauma, targeting glia to reduce tolerance to opioid analgesics, peripheral opioid and nonopioid analgesia, advances in the application of regional anesthesia, a pharmacogenetics approach, and CAM approaches. These therapies will hopefully optimize pain management in future wounded service members. In addition, we recognize the need for retrospective patient studies to assess the clinical outcomes linked to the range of pain treatments received by wounded service members throughout the continuum of care.

DISCLOSURE

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